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Pulmonology FM

The Descartes' lesson: the doubt as part of the clinical reasoning

La lezione di Cartesio: il dubbio come parte del ragionamento clinico

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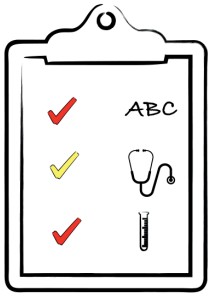

- ✔ 39 year-old male, caucasian, non smoker, living in a subtropical island.
- ✔ low level exposure to molds.
- ✔ familial clinical history: not relevant.
- ✔ past medical history: not relevant.
- ✔ clinical onset: exertional dyspnea persisting for six months.

The patient was admitted to the local hospital where CT scan, bronchoalveolar lavage (BAL) and transbronchial lung cryobiopsy were performed.

Even though the analysis performed on the BAL fluid, collected during the bronchoscopy, stated lymphocytosis (CD4+T cell), a final diagnosis of Lipidic Pneumonia was made and treatment with high dose steroids (prednisone 50 mg/die) was started.

The patient experienced a recurrence of symptoms – including **dyspnea, fever**, and recently, **oral mucosal blisters** – during steroid tapering, despite repeated high doses of steroids and attempts at tapering.
He sought a second opinion while on high-dose steroids.
Upon admission in our Department, the CT scan of the thorax was nearly normal.
Laboratory tests revealed mild anemia (Hb=12.7 g/dL, MCV=90.7 fl), normal C-reactive protein, negative autoimmunity (including myositis autoantibodies and ANCA), negative Bence-Jones proteins and monoclonal components in urine and serum.
Precipitins for molds and avian proteins were also negative.
Pulmonary function tests showed normal lung volumes but a reduced D_{LCO} (Tab. I).
CT scan and cryosamples carried out during the first admission to the Hospital were revised.

Table I. Pulmonary function test - GLI.

		%PRED	z score
FVC	4.95 L	105	0.370
FEV_1	4.37 L	113	1.111
FEV_1/FVC	0.88	108	1.226
TLC	6.51 L	101	0.065
RV	1.65 L	112	0.444
D_{LCO}	**18.8** ml/min/mmHg	**65**	**-2.695**

Clinical history

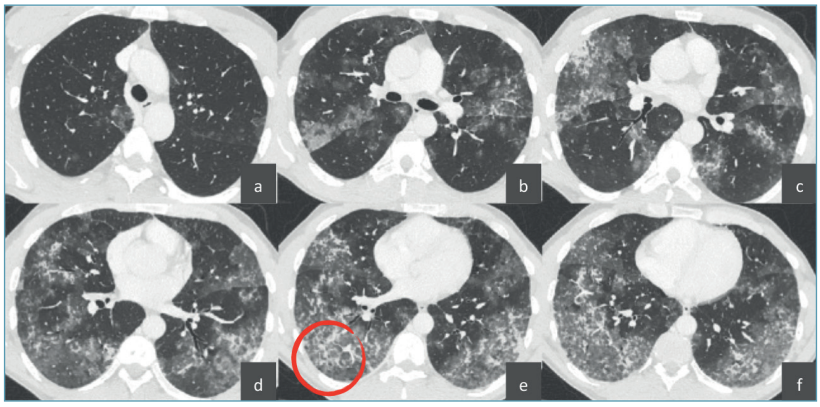

Figure 1. (a-f) Extensive areas of patchy ground glass attenuation in the mid to lower lung zones; (e) Coarse thickening of the interlobular septa and nodules arranged in a branching pattern ( ).

CT scan showed extensive areas of patchy ground-glass attenuation in the mid to lower lung zones, coarse thickening of the interlobular septa and nodules arranged in a branching pattern (Fig. 1).

Bioptic samples (2 mm of larger diameter) showed a significant lymphoid infiltration without cellular atypia, but that could not be better characterized in terms of its phenotype or distribution. Scattered foci of organizing pneumonia and accumulation of foamy macrophages (consistent with lipidic pneumonia) were also identified.

These aspects may suggest a list of histopathologic diagnoses/patterns other than lipidic pneumonia: some kind of lymphoproliferative disorder, hypersensitivity pneumonitis and an association between lipidic pneumonia-alveolar proteinosis/hypersensitivity pneumonitis.

At this point, the clinical differential diagnosis included lymphoproliferative disorders and, less likely, alveolar proteinosis with hypersensitivity pneumonitis, Niemann-Pick type B disease, and GATA2 deficiency with lung manifestations.

A bone marrow biopsy was performed showing only an interstitial mild CD4+ T lymphocytic infiltrate; no elements suggesting a diagnosis of a lipid storage disorder (namely Niemann-Pick disease) or myelodysplastic features were identified.

BAL CD4+ T cell lymphocytosis was consistent also with a granulomatous disorder, however precipitins were negative and CT scan aspects were not typical for a diagnosis of hypersensitivity pneumonitis.

Given the lack of a clear diagnosis, a decision was made: to taper and eventually withdraw the steroid treatment while closely monitoring the patient for recurrence of symptoms (a strategy inspired by the concept of "masterpiece inactivity with compulsive observation" or MICO).

Two months later, after ten days without steroids, the patient was readmitted due to significant and rapidly progressive dyspnea. On admission, he required high-flow oxygen due to acute respiratory failure type I.

Laboratory results showed lymphopenia (610 lymphocytes/mm^3), anemia (Hb=13 g/dL), hypogammaglobulinemia, elevated C-reactive protein (68.7 mg/dL), and slight increases in LDH. Autoimmunity and serum precipitins were again negative.

A new CT scan of the thorax showed diffuse nodularity in both lungs, along with focal areas of ground-glass opacities (Fig. 2).

In light of the rapidly progressive respiratory failure and the need of tissue for diagnostic confirmation during the steroid wash-out period, bronchoscopy with BAL and transbronchial cryobiopsy was performed.

HRCT

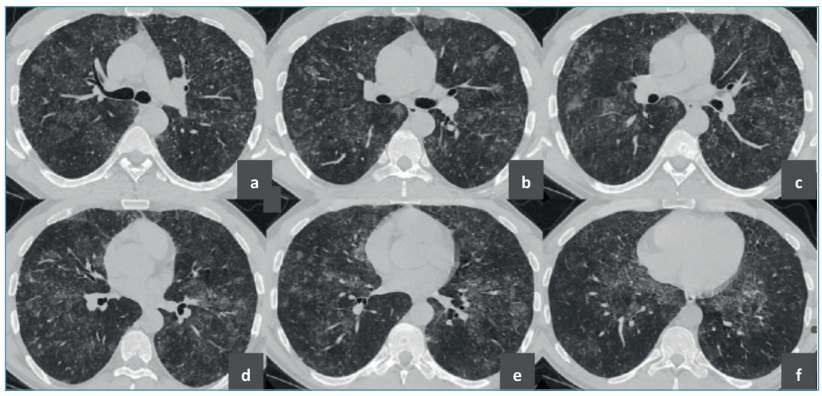

Figure 2. (a-f) Diffuse nodularity along with focal areas of ground glass opacity.

BAL fluid analysis revealed a slight increase in total cell count with a huge CD4+ lymphocytosis (Tab. 2). Microbiological tests for bacteria, fungi and viruses including CMV, EBV, HHV8, HHV6 and others were negative.

Histopathology of the lung samples showed a nodular, angiocentric lymphoid infiltrate, predominantly composed of CD3+ T lymphocytes and histiocytes, with scattered large CD20+ cells (mature B lymphocytes) (Fig. 3). In-situ hybridization for Epstein-Barr virus RNA (EBER) and immunohistochemistry for IgG4 expression were negative.

BAL

Tabella II. BAL fluid analysis.

Total cell count			**299,000 cells/mm^3**	
Macrophages	**Lymphocytes**	**CD3+**	**CD4+**	**CD19+**
3%	**97%**	**96%**	**88%**	**1%**

The suspicion of *Lymphomatoid Granulomatosis (LyG)* grade 1 was raised.
The patient's respiratory condition worsened prompting three i.v. pulses (in three consecutive days) of methylprednidone (500 mg each), with a rapid and significant improvement.

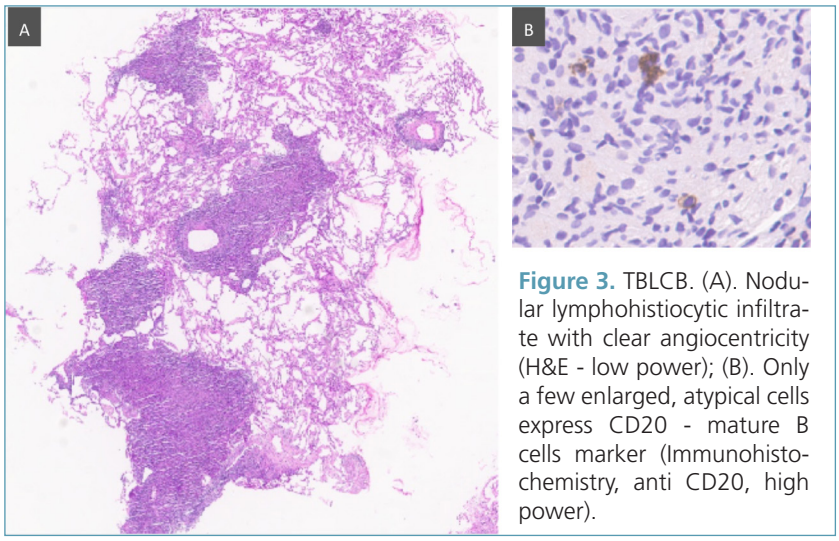

Figure 3. TBLCB. (A). Nodular lymphohistiocytic infiltrate with clear angiocentricity (H&E - low power); (B). Only a few enlarged, atypical cells express CD20 - mature B cells marker (Immunohistochemistry, anti CD20, high power).

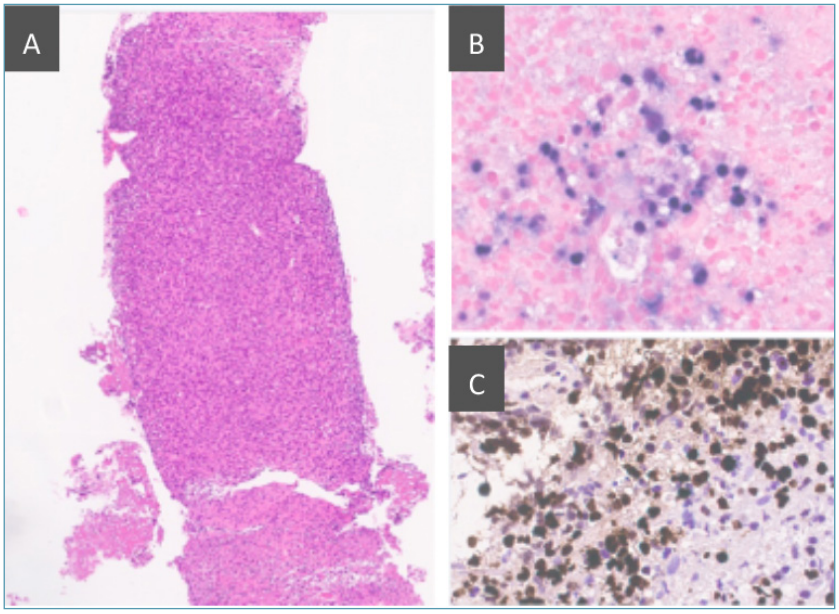

Figure 4. EUS guided needle aspiration biopsy. (A) Atypical lymphoid cells surrounded by necrotic tissue (H&E, low power); (B) In situ hibridization document the presence of EBER+ cells (high power); (C) Cells depicted by anti-CD20 (high power).

One week later a PET-CT scan revealed intense FDG accumulation in the right adrenal gland (SUV=8), with no other significant findings. An esophageal ultrasound-guided biopsy of the right adrenal gland was performed, revealing a lymphoid infiltrate rich in atypical cells, CD20+ and EBER+, embedded in coagulative necrotic tissue (Fig. 4).

Diagnosis

The diagnosis of LyG grade III was finally done.

Discussion

Epstein-Barr virus (EBV), also known as human herpesvirus 4 (HHV-4), is a double-stranded DNA gamma-herpesvirus. The virus is transmitted orally via saliva exchange and reaches the submucosal secondary lymphoid tissues (e.g. tonsils) through epithelial transcytosis. It primarily infects B lymphocytes, preferentially via the CD21/CR2 receptor. After the resolution of primary infection, the virus persists in a small number of memory B cells throughout life, entering, under physiological conditions, a latency stage characterized by restricted expression of viral proteins. Several patterns of latent viral expression are recognized based on the spectrum of proteins and transcripts expressed. These include EBV nuclear antigens (EBNA1, 2, 3A, 3C, LP), latent membrane proteins (LMP1, 2), and small untranslated RNAs (EBERs). EBV-specific CD8+ T cells, which can kill infected B cells, are of utmost importance for EBV-specific immune control.

Lymphomatoid granulomatosis (LyG) is an EBV-associated angiocentric and angiodestructive B-cell lymphoproliferative disorder involving extranodal sites. It occurs in patients lacking evidence of inborn or acquired immune deficiency/dysregulation other than immunosenescence. Lung involvement is required for diagnosis. LyG typically presents in adulthood, between the fourth and sixth decades of life, and rarely occurs in children. The male-to-female ratio is approximately 2:1, and there is no racial predisposition. LyG is almost always an extranodal disease, with nearly all patients presenting with bilateral lung involvement. Other common sites include the central nervous system (brain, 26%), skin (34%), kidneys (19%), and liver (17%). Lymph nodes, spleen, and bone marrow are spared at diagnosis; thus, LyG diagnosis should be questioned if lymph nodes are involved.

Despite universal lung involvement, only 30–60% of patients present with overt respiratory symptoms, and the remaining cases are identified on imaging. Presenting respiratory symptoms are often insidious (e.g.cough, dyspnea, or chest pain), though cases of acute respiratory failure have been reported. Systemic symptoms (fever) or symptoms related to other organs involvement are part of the clinical scenario of the disorder. Lung lesions, often influenced by corticosteroid treatment, may wax and wane, leading to diagnostic delays. Rarely LyG may manifest in the lung with a coexisting infection. Pulmonary imaging typically reveals multiple bilateral lung nodules, frequently in the middle and lower lobes. These nodules vary in size, usually exhibit a peribronchial and vascular distribution, and may display necrosis or cavitation. Laboratory tests are non-specific, with lymphopenia, elevated C-reactive protein and LDH, and hypogammaglobulinemia being the most commonly reported findings. The vast majority of patients show evidence of prior EBV infection (positivity for VCA-IgG).

The most characteristic histologic features are observed in the lung nodules. These consist of a polymorphous mononuclear cell infiltrate with prominent vascular infiltration and frequent necrosis (angiocentric/angiodestructive process). Varying numbers of large, often atypical, CD20+ B lymphocytes are present within a background of numerous CD3+ small T lymphocytes (mainly CD4+) and scattered plasma cells and histiocytes. Evidence of Epstein-Barr virus infection in CD20+ B lymphocytes can be demonstrated in most cases by EBER.

LyG is classified into three histologic grades based on the density of EBV+ B cells. This classification has prognostic and therapeutic implications, as strategies to enhance the host's immune system are typically used for grade 1 and 2 lesions, whereas chemotherapy (DLBCL-like regimens) is required for grade 3 disease. Notably, the number of atypical EBV+ B cells may vary over time and between sites.

The differential diagnosis of LyG includes other lymphoproliferative disorders (IgG4 related disease, multicentric Castlemann disease, extranodal NK/T-cell lymphoma, nasal type), inflammatory or infectious disorders (e.g., ANCA-associated vasculitides, organizing pneumonia, mycobacteria infections) affecting the lung.

LyG pathogenesis likely results from defective local immune surveillance by CD8+ cytotoxic T cells and abnormal immune responses to EBV. The vasculitic changes and tissue necrosis are attributed to direct vessel invasion by inflammatory cells in response to EBV and chemokine-mediated processes (CXCL9 and CXCL10).

This case report teaches us about:

✔ **DANGEROUS CONSEQUENCES OF MISDIAGNOSIS & INAPPROPRIATE TREATMENTS**

A misdiagnosis at the onset can lead to unnecessary investigations and inappropriate treatments (in this case, steroids), which may significantly confound the clinical picture.

✔ **COMMON MISUNDERSTANDINGS LINKED TO RARE DISORDERS**

Rare disorders do not always present with typical features, further complicating the diagnostic process. In this case, the initial CT scan showed a "crazy-paving" pattern, which - according to the anchoring heuristic - is usually associated with conditions such as lipidic pneumonia, alveolar proteinosis, adenocarcinoma, or alveolar hemorrhage. However, this pattern has also been reported, typically alongside nodules or alveolar consolidations, in pulmonary lymphomas (e.g., MALT lymphoma, peripheral T-cell lymphoma, granulomatous mycosis fungoides, and, as in this case, LyG).

✔ **NEED FOR EXPERTISE IN PERFORMING LUNG CRYOBIOPSY**

Lung cryobiopsy should be performed in experienced centers, as obtaining samples with a minimum diameter of 5 mm is essential to ensure their adequacy. Samples that lack specific features are not diagnostically useful.

✔ **GREAT VALUE OF MULTIDISCIPLINARY DISCUSSION**

The multidisciplinary approach is nowadays the rule of thumb mainly when doctors are dealing with complex cases.

✔ **DIAGNOSTIC AND THERAPEUTIC STRATEGIES: HANNIBAL'S LESSON**

This clinical case serves as a fascinating example of how diagnostic and therapeutic strategies can draw inspiration from historical documents, from military tactics, specifically the Battle of Cannae. In this battle, Hannibal outmaneuvered a numerically superior Roman army near the ancient village of Cannae, in southern Apulia (modern Puglia, Italy), in early August 216 BC, Hannibal achieved victory by deliberately weakening the center of his forces compared to the flanks, luring the Roman forces into a "cul-de-sac" that narrowed their front and ultimately led to their encirclement and defeat.

Similarly, this case underscores the importance of maintaining a broad differential diagnosis, even when findings appear characteristic. The strategic pause in steroid therapy, though challenging for the patient, was pivotal in uncovering the diagnosis.

✔ **THE DOUBT AS PART OF CLINICAL REASONING**

Renè Descartes devoted his life to Mathematics, Physics, and Philosophy. His fundamental contribution to knowledge was the application of methodical doubt, dismissing apparent knowledge derived from authority or the senses. This methodological doubt should always be a part of the clinical reasoning applied when "doctors think".

This case report is dedicated to the memory of Angelo Carloni, a brilliant thoracic Radiologist, whose humanity, humour, and expertise made him an unforgettable friend and mentor.

References

Bocchiola M, Sartori M. La battaglia di Canne. Torino: Utet 2017.

Colby TV, Carrington CB. Lymphoreticular tumors and infiltrates of the lung. Pathol Annu 1983;18:27-70.

Deckert M, Brunn A. Lymphomas and haematopoietic neoplasms. In: Smith C, Perry A, Kovacs GG, Jacques TS (Eds). Greenfield's neuropathology, 10e. Boca Raton: CRC Press 2025;Vol II:1757-1783.

Gewurz BE, Longnecker RM, Cohen JI. Esptein-Barr virus. In: Howley PM, Knipe DM, Damania BA, Cohen JI (Eds). Fields virology: DNA viruses. Philadelphia: Lippincott Williams & Wilkins (LWW) 2022:324-388.

Kaztenstein AL, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. Cancer 1979;43:360-373. https://doi.org/10.1002/1097-0142(197901)43:1<360::aid-cncr2820430151>3.0.co;2-8

Nicolae A, Pittaluga S, Said JW. Virally associated B-cell lymphoproliferative disease. In: Jaffe ES, Arber DA, Campo E, et al. (Eds): Hemopathology, 3e. Elsevier 2024:585-608.

Poletti V, Piciucchi S, Asioli S. Lymphoproliferative diseases involving the lung. In: Grippi MA, Antin-Ozerkis DE, Dela Cruz CS, et al. (Eds). Fishman's Pulmonary Diseases and Disorders, 6e. New York: MacGraw Hill Education 2023:2045-2068. https://accessmedicine.mhmedical.com/content.aspx?bookid=3242&sectionid=270614380

Sakuma I, Ishibashi R, Matsue K, et al. Primary adrenal insufficiency due to lymphomatoid granulomatosis in a 32-year-old man. Lancet 2024;430:e3. https://doi.org/10.1016/S0140-6736(24)00974-7

Sverzellati N, Poletti V, Chilosi M, et al. The crazy-paving pattern in granulomatous mycosis fungoides: high-resolution computed tomography-pathological correlation. J Comput Assist Tomogr 2006;30:843-845. https://doi.org/10.1097/01.rct.0000214269.72180.64

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Conflitto di interessi
Gli autori dichiarano di non avere nessun conflitto di interesse con l'argomento trattato nell'articolo.

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